3-5-2019

Risks and Benefits of Administering Bisphosphonates with a Diagnosis of Atypical Osteoporotic Fracture

Molly Beyer

Risks and Benefits of Administering Bisphosphonates with a Diagnosis of Atypical Osteoporotic Fracture

Molly Beyer, BSN, RN

Family Nurse Practitioner Program

University of North Dakota

PERMISSION

Title

Department Nursing

Degree Master of Science

In presenting this independent study in partial fulfillment of the requirements for a graduate degree from the University of North Dakota, I agree that the College of Nursing & Professional Disciplines of this University shall make it freely available for inspection. I further agree that permission for extensive copying or electronic access for scholarly purposes may be granted by the professor who supervised my independent study work or, in his/her absence, by the chairperson of the department or the dean of the Graduate School. It is understood that any copying or publication or other use of this independent study or part thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of North Dakota in any scholarly use which may be made of any material in my independent study.

Signature _Molly Beyer_____

Date ___3/6/2019_____

Abstract

Osteoporosis is associated with an increased risk for atypical fractures (Dunphy, Winland-Brown, Porter & Thomas, 2015). It is a disease affecting eight-million women and two-million men in the United States of America. This disease is largely associated with advanced age, female gender and other comorbidities, and proper treatment is essential. Multiple treatment modalities are available, both pharmacologic and non-pharmacologic (Lindsay & Cosman, 2018). Recommendations for prevention of osteoporotic fracture are prevalent, but recommendations regarding pharmacologic treatment in the post-operative period is lacking. One pharmacologic treatment, Bisphosphonate (BP) therapy, remains controversial; as evidence regarding safety for patients in the post-operative recovery period is minimal (Cho et al., 2015). The following is a case analysis with a thorough literature review highlighting the risks and benefits of administering BP therapy to osteoporotic patients in the post-operative period.

Risks and Benefits of Administering Bisphosphonates with a Diagnosis of Atypical Osteoporotic Fracture

Background

Osteoporosis

Osteoporosis is a reduction in bone strength that leads to deterioration of human skeletal framework and is associated with an increased risk for fractures (Dunphy, Winland-Brown, Porter & Thomas, 2015). A clinical diagnosis of osteoporosis is identified by a bone mineral density (BMD) of 2.5 standard deviations (SD) below the mean for healthy adults; the BMD is measured radiographically via the dual energy x-ray absorptiometry (DXA) scan in the lumbar spine, total hip or femoral neck, and is also known as the T-score (Lindsay & Cosman, 2018).

The development of osteoporosis is largely based on nonmodifiable and potentially modifiable risk factors. Nonmodifiable risk factors include female gender, advanced age, Caucasian race, genetics, comorbid dementia and personal history of fracture as an adult. Potentially modifiable risk factors include tobacco use, a history of glucocorticoid use, estrogen deficiency, inadequate nutrition hindering calcium and vitamin D intake, alcoholism, falls and inadequate physical activity (Lindsay & Cosman, 2018).

With osteoporosis comes an increased risk for atypical osteoporotic fractures, which often require surgical intervention for repair. The practitioner’s goal for treatment of patients with osteoporosis is to prevent and manage acute fractures, while treating the underlying disease process. The first step in treating osteoporosis is to reduce the impact of modifiable risk factors such as those listed previously in this paper. Lifestyle changes regarding nutrition intake and physical activity are typically involved in the plan of care. Pharmacologic interventions are also utilized; these include Vitamin D and Calcium supplementation, Selective Estrogen Receptor

Modulators (SERMs), hormone replacement therapy (HRT) and bisphosphonates (BP). These medications are Food and Drug Administration (FDA) approved for the prevention and treatment of osteoporosis (Lindsay & Cosman, 2018).

Bone Remodeling

This paper is largely focused on the effects of BP activity on bone recovery. Understanding the mechanism of action of BP therapy requires knowing how the human body performs bone-turnover or remodeling following a fracture. Bone remodeling involves the combined activity of cells called osteoclasts and osteoblasts. Osteoclasts are multinucleated cells that remove damaged bone and resorb calcified bone matrix during bone remodeling. Osteoblasts are cells that secreted organic components into the bony matrix to synthesize the formation of bone (Mescher, 2018). Effective bone remodeling requires continuous resorption of bone tissue equal to the amount of new bone being laid down at a given site. Following the fracture of a bone, blood vessels form a clot around the site which is eventually replaced by a hard callus created by osteoblasts. Eventually the callus is invaded by the vasculature, allowing osteoclasts to enter the area to resorb the hard callus into woven bone. A secondary remodeling phase follows, which includes more resorption by osteoclasts, remodeling of the original fractured bone below the callus, and formation of laminar bone via osteoblasts. (Lindsay & Cosman, 2018; Kates & Ackert-Bicknell, 2016).

Bisphosphonates work to combat osteoporosis by directly impairing osteoclast resorption function. They also work to reduce the presence of osteoclasts in the human body by apoptosis (Lindsay & Cosman, 2018). Use of BP therapy is controversial because of the potential theoretical risk of suppression of bone turnover and impairment of bone remodeling (Koh,

Guerado, & Giannoudis, 2017). In theory, the use of BP could interfere with fracture healing in patients with osteoporosis due to decrease osteoclast function (Cho et al., 2015).

Purpose

The purpose of this paper is to identify what risks or benefits, if any, there are in administering BP therapy to patients with a clinical diagnosis of atypical osteoporotic fracture requiring surgical intervention. Accompanying a thorough literature review is a case study involving a seventy-two-year-old woman, with a recent diagnosis of atypical femoral fracture, who presents to the clinic following surgical repair.

Case Report

A seventy-two-year-old female presents to the outpatient clinic for a follow-up evaluation. She was recently discharged from the hospital after a three-day-stay after an open reduction and internal fixation (ORIF) of her right hip, originating from an at-home fall. Her past medical history includes Chronic Obstructive Pulmonary Disorder (COPD), Anemia, Hypertension, Hypercholesterolemia and tobacco use, one pack per day for forty-five years. Her current medications include Fluticasone-propionate and salmeterol, Metoprolol, Quetiapine and Iron sulfate, twice a day, and Losartan, Paroxetine, Lipitor and a multivitamin, daily. Most recently she completed a Prednisone taper following an acute COPD exacerbation. A thorough social history reveals she is widowed, lives alone, follows a dairy-free diet, and performs daily home exercises she learned at physical therapy, of which she completed a week ago.

Review of her symptoms finds she is “feeling more tired than usual”, is experiencing a new-onset poor appetite, and occasional pain in her right hip, rated a 3/10, occurring before bed, described as aching, exacerbated by overuse and relieved by acetaminophen and rest. Physical examination reveals a normal exam, with full range of motion, good strength, balance and

reflexes in bilateral lower extremities. Visualization of her surgical incision shows a well-healing, approximated incision, negative for swelling, drainage, erythema or pain with palpation.

Assessment of the patient's risks for fracture including age, post-menopausal state, chronic tobacco use, dairy-free diet and history of glucocorticoid use prompted further evaluation to determine the etiology of her right hip fracture. A dual energy x-ray absorptiometry (DXA) scan was ordered to assess her bone mineral density and the results of the scan are were a T-score of -2.6, which is diagnostic of osteoporosis. Her agreed-upon treatment plan included supplemental administration of Calcium, 1,200 mg, and vitamin D, 800 international units daily and incorporating a daily oral bisphosphonate, while continuing at-home exercises and joining her local Silver Sneakers program. Follow-up evaluation of her physiologic response to her treatment included a plan to reassess her bone mineral density with a repeat DXA scan in two years.

Literature review

In conducting a literature review, articles were reviewed using the Cumulative Index of Nursing and Allied Health Literature (CINAHL), MEDLINE Complete, Pubmed and Pubmed Central (PMC) databases. Limitations applied to the search included available articles published within five years (2014-2019), pertaining to the adult population, of whom experienced an atypical osteoporotic long-bone fracture, was treated with surgical repair and received bisphosphonates in the pre- or post-operative periods. These criteria revealed a narrow amount of information, so the search was expanded to include surgical repair of osteoporotic joints, which yielded outcomes of bisphosphonate use with osteoporotic knee and hip arthroplasties; a total of eleven articles were utilized in this review.

Summary of Findings

Utilizing the Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence (2011), eleven articles were evaluated, and the findings summarized. The levels are evidence are rated from level 1 to 5: level 1 evidence is systematic reviews of randomized control trials (RCT), individual RCT and meta-analyses. Level 2 evidence is from systematic reviews of cohort studies and individual cohort studies, level 3 evidence stems from review of case-control studies and individual case-control studies, level 4 evidence includes case series, case control and poor-quality cohorts, and finally, level 5 evidence includes expert opinions, experimental research and animal studies. The level of evidence is most credible with a level 1 rating (Howick et al., 2011).

Level 1 evidence from a meta-analysis of 2,500 patients with differing osteoporotic fractures found that anti-osteoporotic medications such as BPs, which possess antiresorptive activity, showed no clinically significant delay in fracture healing and are safe to be given in the pre- and post-operative period to reduce the incidence of future fractures (Bartl, Stengel, Gulke, & Gebhard, 2016). Li, Cai & Zhang (2015) formed a meta-analysis evaluating for a delay in healing based on clinical and radiologic findings and bone-turnover markers. This is another example of level 1 evidence that patients treated with BP therapy less than three months post-operatively had no significant differences in healing time when compared to non-BP-users. Recommendation was made for BP therapy to be started immediately following surgical repair as there was also level 1 evidence this would prevent subsequent fractures. (Li et al., 2015).

Ng, Yue, Joseph & Richardson (2014) found level 2 evidence found stating that initiating BP therapy at different times following an atypical osteoporotic fracture showed no difference in healing time. The benefit of BP therapy for prevention of future fractures in such patients outweighs risk of non-union (Ng, Yue, Joseph & Richardson, 2014). Kates & Ackert-Bicknell

(2016) also found level 2 evidence of no delay in bone-union with initiation of BPs immediately after diagnosis of an atypical osteoporotic long-bone fracture. Patients already on long-term BP therapy had a delay in bone-union 26% of the time, however, insufficient data prevented the analysis from being fully understood (Kates & Ackert-Bicknell, 2016). Xue Li, Chen, Yan & Pan (2014) evaluated the treatment of patients with BPs during bone healing and level 1 evidence showed there is no association with BP use, delay in direct bone healing or fracture nonunion. Also, delaying the administration of BPs following a confirmed atypical osteoporotic fracture had no effect on bone healing. Finally, this meta-analysis confirmed recommendations that treatment BPs should be done after the first osteoporotic fracture to increase bone mineral density and reduce the risk of future fractures (Xue et al., 2014).

A case-control study compared outcomes of bisphosphonate naïve patients who were administered BPs any time during a twenty-four-month post-operative period with BP naïve patients who were non-users of these drugs. The rate of new clinical fracture was found to be increased in BP users during the first six months of treatment, the difference eventually decreasing over time, and by month eighteen, the rate of fracture was similar for both cohorts. Level 3 evidence was used to support administering BPs as beneficial to the patient upon clinical diagnosis of an atypical osteoporotic fracture (Bergman, Nordström & Nordström 2018). Alternatively, Prieto-Alhambra et al. (2014) found level 3 evidence suggesting osteoporotic patients who received total knee or hip arthroplasties and became BP users for at least six months in the post-operative period had a fifty-nine percent reduced risk for surgical revision (Prieto-Alhambra et al., 2014).

Level 3 evidence states there is no statistical evidence to support delayed or non-healing bone following repair of an osteoporotic fracture. Recommendation was made for patients who

have taken BPs for five years or more, that they may have an increased risk for a decrease in bone formation and remodeling, therefore requiring surgery to be performed by experienced surgeons. Further, a suggestion was made for patients to have a 'drug holiday' after five years of BP therapy to prevent such complications (Phillips, Harrison, Akrawi & Sidhom, 2017). These findings are somewhat contradictory to Koh, Guerado & Giannoudis (2017) who found level 2 evidence of no significant different in length of healing time in comparing patients taking BPs for less than five years versus patients taking BPs greater than five years. It also suggests there is no clinically significant risk of revisional surgery in either of these patient groups (Koh, Guerado & Giannoudis, 2017).

In comparing patients with osteoporotic intertrochanteric fractures who received BP therapy at either one week, one month or three months following surgical repair, the time of bone union, as evidenced by radiographic callus formation, there was no significant difference in bone union. This confirmed level 2 evidence that delaying initiation of BPs in the post-operative period does not affect the length of healing time. Subsequently, early administration of BPs was found to prevent future osteoporotic fractures (Cho et al., 2015).

Finally, a study comparing osteoporotic patients with atypical fractures of the proximal humerus were evaluated for length of time for radiographic bone-union when receiving BP therapy starting at either two weeks or three months into the post-operative period. Level 2 evidence found that delaying BP treatment does not significantly affect healing outcomes in these patients (Seo, Yoo, Ryu & Yu, 2016).

Recommendations for Practice

- Use of bisphosphonates in the post-operative period does not increase healing time or prevent bone-union in surgically repaired atypical osteoporotic fractures.

- Delaying administration of bisphosphonates is not beneficial in patients with a confirmed clinical diagnosis of atypical osteoporotic fracture, who are having surgical repair.
- Administering bisphosphonates to patients with a confirmed clinical diagnosis of atypical osteoporotic fracture is beneficial in preventing future fractures.

Conclusion

Osteoporosis remains a major health concern among post-menopausal women and at this time, BP therapy is the most widely used treatment for it (Li et al., 2015). With thoughtful consideration of information found in the thorough literature review, recommendations for practice can be made for administration of BP's with a concurrent diagnosis of atypical osteoporotic fracture as it relates the case presented. Although there was a variety of level one evidence regarding the benefit of BP's immediately upon diagnosis, the risk of impaired bone healing is still somewhat unknown. Until stronger research is presented regarding impaired bone healing, the benefit of anti-osteoclastic activity associated with BP use outweighs hypothesized risk.

References

Bartl, C., Stengel, D., Gulke, J., & Gebhard, F. (2016). Clinical results following conservative and surgical treatment of osteoporotic distal radius fractures in the elderly: Overview of best available evidence. [Klinische Ergebnisse nach konservativer und operativer Therapie der distalen Radiusfraktur beim alteren Patienten: Ubersicht der besten verfugbaren Evidenz] Der Unfallchirurg, 119(9), 723-731. doi:10.1007/s00113-016-0216-y [doi]

Bergman, J., Nordström, A., & Nordström, P. (2018). Bisphosphonate use after clinical fracture and risk of new fracture. Osteoporosis International, 29(4), 937–945. https://doi-org.ezproxylr.med.und.edu/10.1007/s00198-017-4367-7

Cho, Y. J., Chun, Y. S., Rhyu, K. H., Kang, J. S., Jung, G. Y., & Lee, J. H. (2015). Does the time of postoperative bisphosphonate administration affect the bone union in osteoporotic intertrochanteric fracture of femur? Hip & Pelvis, 27(4), 258-264. doi:10.5371/hp.2015.27.4.258 [doi]

Dunphy, L., Winland-Brown, J., Porter, B. & Thomas, D. (2015). Primary care: The art and science of advanced practice nursing, (4th ed.). Philadelphia, PA: F. A. Davis Company.

Kates, S. L., & Ackert-Bicknell, C. L. (2016). How do bisphosphonates affect fracture healing? Injury, 47 Suppl 1(0 1), S65-8.

Koh, A., Guerado, E., & Giannoudis, P. V. (2017). Atypical femoral fractures related to bisphosphonate treatment: Issues and controversies related to their surgical management. The Bone & Joint Journal, 99-B(3), 295-302. doi:10.1302/0301-620X.99B3.BJJ-2016-0276.R2 [doi]

Li, Y.-T., Cai, H.-F., & Zhang, Z.-L. (2015). Timing of the initiation of bisphosphonates after surgery for fracture healing: a systematic review and meta-analysis of randomized controlled trials. Osteoporosis International, 26(2), 431–441. https://doi-org.ezproxylr.med.und.edu/10.1007/s00198-014-2903-2

Lindsay, R., & Cosman, F. (2018). Osteoporosis. In J. L. Jameson, A. S. Fauci, D. L. Kasper, S. L. Hauser, D. L. Longo & J. Loscalzo (Eds.), Harrison's principles of internal medicine, (20e). New York, NY: McGraw-Hill Education.

Howick, J., Chalmers, I., Glasziou, P., Greenhalgh, T., Heneghan, C., Liberati, A. & Moschetti, I. (2011). The oxford 2011 levels of evidence. *Oxford center for evidence-based medicine*. Retrieved from https://www.cebm.net/2016/05/ocebm-levels-of-evidence/

Mescher, A. L. (2018). Bone. Junqueira’s basic histology: Text and atlas, (15e). New York, NY: McGraw-Hill Education.

Ng, A. J., Yue, B., Joseph, S., & Richardson, M. (2014). Delayed/non-union of upper limb fractures with bisphosphonates: Systematic review and recommendations. ANZ Journal of Surgery, 84(4), 218-224. doi:10.1111/ans.12536

Phillips, H. K., Harrison, S. J., Akrawi, H., & Sidhom, S. A. (2017). Retrospective review of patients with atypical bisphosphonate related proximal femoral fractures doi://doi-org.ezproxylr.med.und.edu/10.1016/j.injury.2017.03.025

Prieto-Alhambra, D., Lalmohamed, A., Abrahamsen, B., Arden, N. K., de Boer, A., Vestergaard, P., & de Vries, F. (2014). Oral bisphosphonate use and total knee/hip implant survival: Validation of results in an external population-based cohort. Arthritis & Rheumatology (Hoboken, N.J.), 66(11), 3233-3240. doi:10.1002/art.38789 [doi]

Seo, J. B., Yoo, J. S., Ryu, J. W., & Yu, K. W. (2016). Influence of early bisphosphonate administration for fracture healing in patients with osteoporotic proximal humerus fractures. Clinics in Orthopedic Surgery, 8(4), 437-443. doi:10.4055/cios.2016.8.4.437 [doi]

Xue, D., Li, F., Chen, G., Yan, S., & Pan, Z. (2014). Do bisphosphonates affect bone healing? A meta-analysis of randomized controlled trials. Journal of orthopaedic surgery and research, 9, 45. doi:10.1186/1749-799X-9-45